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09/380,738	12/06/1999	ERIC C. REYNOLDS	040268/0161	3015

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/380,738	Applicant(s) REYNOLDS, ERIC C.
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,9-11,15-26 and 41-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-7, 9-11, 15-26, 41-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 23 (filed 12/24/02), claim 3 has been cancelled, and claims 1, 6, 7, 9, 50 amended. Claims 1, 2, 4-7, 9-11, 15-26, 41-61 are pending.

Applicants' arguments have been considered and found not persuasive.

Applicants' election of Group V is acknowleged. However, neither of claims 15 or 16 is withdrawn at this time.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is asserted in claim 17 that the claimed complex is effective to co-localize calcium ions, fluoride ions and phosphate ions at a "target site". Certainly, if one applies the claimed complex to a given site "X", whatever calcium ions, fluoride ions and phosphate ions may be present in the complex will be present at site "X", at least temporarily. But the claim could be interpreted in other ways. In particular, the claim could be interpreted to mean

that Ca^{++}, F^- and $HPO_4^=$ ions in addition to those initially present in the complex will be attracted to the site by some sort of chemotaxis. The claim also implies that other cations and anions will also be attracted to the site. However, there is no evidence that this is the case, and no reason to expect that this will occur. In addition to the foregoing, the claim encompasses the possibility of administering the complex to one location, and consequently attracting cations and anions to some other location. Thus, the claim would encompass the possibility of administering the complex orally, and consequently "localizing" ions in the feet, for example. However, there is not guidance or direction as to how one might accomplish this.

Claim 21 is drawn to a "therapeutic composition". Presumably it is being asserted that the claimed compositions can be used to effectively treat a patient who is suffering tooth decay. However, there is no evidence that this is the case. Possibly it is true that if a composition containing calcium and phosphopeptide is prepared under acidic conditions, then it is very effective at reversing the process of tooth decay. But applicants have argued that their invention specifically excludes such compositions. Accordingly, enablement is lacking for the claimed invention.

*

Claims 1, 2, 4-7, 9-11, 15-26, 41-61 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention.

- Claim 1 recites the following:
  "wherein said complex is formed by binding ... with phosphopeptide".
  It is unclear which phosphopeptide is intended here. It is suggested that the definite article (*the*) or *said* be inserted prior to "phosphopeptide".

- Claim 9 contains an obvious error; however, it is not clear how applicants would most prefer to rectify it.

- Claim 15 recites the phrase "up to about 9.0". This renders the claim indefinite as to the actual upper limit of pH. It is suggested that the qualifier "about" be deleted. See also claim 50.

- It is asserted in claim 17 that the claimed complex is effective to co-localize calcium ions, fluoride ions and phosphate ions at a "target site". What is unclear is how the "target site" relates to the site of co-localization. For example, if the complex were applied to the scalp, could the ions subsequently localize in the kneecaps?

- Claim 20 recites "an anticariogenic composition [which includes] the composition of claim 19". In what way is the composition of claim 20 different from that of claim 19...? It is suggested that applicants explain the difference in physical terms; alternatively it is suggested that claim 20 be cancelled.

- Claim 21 recites "a therapeutic composition [which includes] the composition of claim 19". In what way is the composition of claim 21 different from that of claim 19...? It is suggested that applicants explain the difference in physical terms; alternatively it is suggested that claim 21 be cancelled.

- Claim 21 is indefinite as to the intended "therapeutic" uses.

- Claim 22 is drawn to a "dietary supplement [which includes] the composition of claim 19". Given the phrasing of the claim, it would appear that claim 22 mandates the presence of a compound or composition which is not required by claim 19. What then is the nature of this compound or composition...? Is it a carrier, is it a gelatin capsule, or is it something else? See also claim 23 which permits the presence of some unidentified component that accounts for 99% of the composition.

- Claim 23 encompasses the possibility of the complex "comprising" fully 100% of the dietary supplement. For this embodiment, what exactly is the difference between the dietary supplement of claim 23, and the complex of claim 1...?

- The distinction between claim 25 and claim 26 is unclear. As a first step in the dialog, applicants are requested to provide a few examples of intended anatomical sites of administration other than the teeth or gums.

- Claim 44, line 1 recites "suffered". It appears that the verb form *suffering* is intended instead.

- Claim 44 is indefinite as to the process steps and endpoint. It is suggested that the claim recite that the complex is administered for a time and under conditions effective to promote calcium absorption. The following is an example of claim language which could be used:

  A method for promoting calcium absorption comprising administering to a subject suffering from calcium deficiency or calcium maladsorption a complex according to claim 7 for a time and under conditions effective to promote calcium absorption in said subject.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 4-7, 9-11, 16-26, 41-61 are rejected under 35 U.S.C. §103 as being unpatentable over Reynolds WO 94/00146 or Reynolds (*J. Dent. Res.* **74**(6) 1272, 1995).

Each of the two references teaches a mixture of calcium phosphate and peptide comprising the sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu.

The principle issue in this case is what the claims do require, or do not require, with respect to the ionization state of (a) the phosphopeptide and (b) the calcium phosphate in the final product. As such, one can argue that there are three categories of compositions; these are designated categories "A", "B1: and "B2":

(a) Category "A", in which the claims unambiguously mandate that the final product must have resulted from an alkaline mixture,

(b) Category "B1", in which a mixture of calcium phosphate and phosphopeptide was briefly subjected to an alkaline pH, but then the pH was subsequently lowered, and

(c) Category "B2", in which a composition within "category A" is dissolved in an aqueous solution at an acidic pH, thereby "undoing" whatever effects resulted from previous exposure to alkaline medium.

Consider first claim 16. This claim is rejected, while claim 15 is not. Claim 15 mandates that one actually raise the pH to above pH 7; claim 16, by contrast, does not necessarily require this. Claim 15 recites the following:

15. A method of producing a stable soluble calcium phosphate complex comprising phosphopeptide-stabilized amorphous calcium phosphate wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5), and said amorphous calcium phosphate is formed in alkaline conditions comprising the steps of:

(i) obtaining an aqueous solution... {as recited}

(ii) admixing the solution of step (i) with ...{as recited}

(iii) filtering the mixture resulting from step (ii);

(iv) drying the mixture of step (iii), and

(v) isolating the stable calcium phosphate complex.

Claim 15, however, does not "consist" of the recited steps, it comprises them. As such, claim 15 could encompass the following (claim 200):

200. A method of producing a stable soluble calcium phosphate complex comprising phosphopeptide-stabilized amorphous calcium phosphate wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5), and said amorphous calcium phosphate is formed in alkaline conditions comprising the steps of:

(i) obtaining an aqueous solution... {as recited}

(ii) admixing the solution of step (i) with ...{as recited}

(iii) filtering the mixture resulting from step (ii);

(iv) drying the mixture of step (iii),

(v) dissolving the mixture of step (iv) in aqueous solution buffered to pH 6.5;

(vi) lyophilizing the mixture of step (v) to form a stable calcium phosphate complex, and

(vii) isolating the stable calcium phosphate complex.

Thus, the "stable calcium phosphate complex" formed by this process is no different from the prior art composition, since the mixture was exposed to acidic pH prior to its isolation. Thus, while some of the compositions of claim 16 may be novel, many of them are not. One might ask why a chemist would want to raise the pH to, e.g., 7.5, only to lower it to pH 6.5 later. Were the claims at issue drawn to a method of making the composition, that would be a fair question. But the claims at issue are drawn to a composition *per se*; as such, the question is, what exactly is the difference between a composition which is taken to e.g., pH 6.5 and then lyophilized versus a composition which is taken to e.g., pH 7.5, then down to pH 6.5, then lyophilized? In applicants' arguments and the declaration, the only comparison which has been considered thus far is that of a "first" composition and a "second" composition, wherein the ionization state of the components of the "first" composition is different from the ionization state of the components of the "second" composition. In

other words, this is not simply a question of chemistry, but is also a question of claim interpretation.

It may be the case that applicants believe that there is some sort of "memory" effect on the part of the calcium phosphate and the phosphopeptide, i.e., that once they are exposed to a pH of 7.01 for a few seconds, their structure is forever altered. It seems unlikely that this would be true, but the simplest experiment would be to prepare a solution of the calcium phosphate and the phosphopeptide at a pH of e.g., 6.5, then divide the solution into two equal parts. The "first" mixture is left untreated, and a small quantity of NaOH is then added to the "second" mixture so that the pH (of the "second" mixture) is raised to, e.g., 8.0. After a few minutes, a small quantity of HCl is then added to bring the pH (of the "second" mixture) back down to 6.5. While acknowledging that there would be a slightly higher concentration of NaCl in the "second" mixture than in the "first", it seems rather unlikely that the properties of the "second" mixture would be superior to those of the "first" mixture, specifically with regard to anticariogenic potency. However, if applicants were to undertake such an experiment, and could demonstrate such a "memory" effect with respect to anticariogenic potency, a declaration evidencing this might be sufficient to overcome this rejection. Alternatively, the claim language could be modified. Consider, for example, claim 201 below:

201. A stable, soluble calcium phosphate complex that comprises amorphous calcium fluoride phosphate and a phosphopeptide, wherein said phosphopeptide includes the amino acid sequence Ser(P)-Ser(P)-Ser(P)-Glu-Glu (SEQ ID NO: 5),
and wherein said stable, soluble calcium phosphate complex is prepared by a process which comprises the following steps:

(i) obtaining an aqueous solution... {as recited in claim 15}

(ii) admixing the solution of step (i) with a solution comprising calcium ions, inorganic phosphate and optionally fluoride at a pH of above 7 up to 9.0;

(iii) removing water from the mixture of step (ii), to form a stable calcium phosphate complex, and

(iv) recovering the stable calcium phosphate complex of step (iii).

This claim (claim 201) requires that the calcium phosphate complex which is recovered is that which was exposed to the alkaline pH, which contrasts with what is permitted by the current rendition of claim 1.

Consider next composition claims 46-47. These claims encompass toothpaste and mouthwash. As it happens, Reynolds ('146) provides examples of both these compositions. On page 8 is an example of a mouthwash formulation; the pH is 6.5. The first point to be made is that this disclosure supports the assertion that a pH of 6.5 is a reasonable one for mouthwash. The question then becomes, if one takes a formulation which has been prepared at, e.g., pH 7.01 as recited in the instant claims, and dissolves that in a pH 6.5 solution, can the resulting composition be distinguished from that of Reynolds ('146) by any criterion which has been disclosed in the instant specification? In particular,

will the anticariogenic potency be any different for each of the two compositions? The likelihood is that the ionization state will be determined by the pH of the solution, not by some previous ionization state prior to dissolution. Consider also claims 53, 54, 60 and 61. In these claims there is a very explicit recitation of an acidic pH. Applicants have made no attempt to provide evidence of "unexpected results" for these compositions.

Consider next page 9 of Reynolds (WO 94/00146). This provides an example of toothpaste formulations. It is recited that the pH is within the range of 6-9. This range of 6-9 can be viewed as a Markush Group of 30 members (i.e., 6.0, 6.1, 6.2 ... 8.8, 8.9, 9.0). Of these 30 "members", 19 of them, or 63% fall within the "alkaline" range; 37% fall within the neutral or acidic range. Thus, if a practioner of the Reynolds ('146) invention were to select a pH at random, the probability of selecting an embodiment within the claimed genus is well above 50%.

*

Claims 1, 2, 4-7, 9-11, 16-26, 41-61 are rejected under 35 U.S.C. §103 as being unpatentable over Reynolds (*Proceedings of the Nutrition Society of Australia* **19**, 95-102, 1995) or Holt (*Biochem J.* **314**, 1035, 1996).

Each of Reynolds and Holt teaches at least one of the claimed sequences together with calcium phosphate. The references do not mandate that the compositions were exposed to pH 7.01 at some point in the past. However, it would have been obvious to one of

ordinary skill that if the claimed composition were exposed briefly to a pH of 7.01, and then subsequently exposed to a pH of 6.99, the anticariogenic properties of the composition would be the same as if the composition were only exposed to the latter pH.

Thus, the claims are rendered obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600